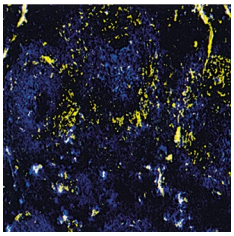
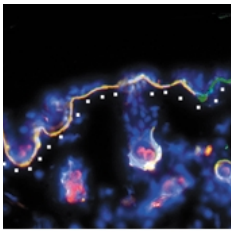
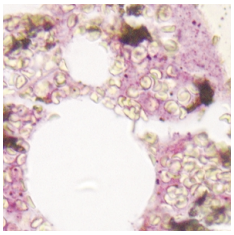


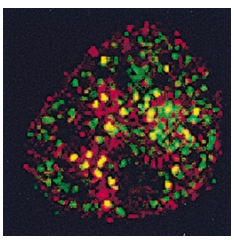
Hormones and autoimmunity. In addition to playing a critical role in lactation, prolactin is thought to affect cells of the immune system and augment autoimmunity. Both B and T cells express prolactin receptors, and the hormone has been shown to influence T cell development and proliferation. Focusing on the effects of prolactin on B cells, Betty Diamond and colleagues found (see pages 275–283) that a two-fold increase in prolactin can break tolerance to certain self-antigens and induce lupus-like disease in a transgenic mouse model. Increased prolactin levels affected B cell development and maturation, and promoted the survival of high-affinity autoreactive B cells that would normally undergo deletion. While these alterations were consistently observed in one genetic background, they were not seen in a second mouse strain, suggesting that susceptibility to hormone-mediated autoantibody development is genetically determined.



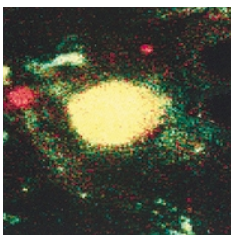
Fibroblasts to the rescue. Dystrophic epidermolysis bullosa refers to a family of severe skin disorders caused by mutations in the type VII collagen gene (*COL7A1*). Patients lack anchoring fibrils that ensure adhesion of the epidermis to the dermis and develop subepidermal blisters in response to minor mechanical stress. The current lack of treatment is an impetus to develop gene therapy strategies that will restore anchoring fibrils. Paul Khavari and colleagues have focused on fibroblasts, cells that can be easily isolated from patients, manipulated ex vivo, and readministered. As they now report (pages 251–255), intradermal injection of fibroblasts engineered to overexpress COL7A1 into patient skin transplanted onto a mouse was able to restore anchoring fibrils and prevent blistering.



Mobilization mechanisms. Hematopoietic progenitor cells, which have the ability to reconstitute the blood and immune systems, reside primarily in the bone marrow. However, they can be mobilized into the circulation by cytokines, and peripheral blood-derived progenitor cells are used for the majority of hematopoietic rescue transplants. Studying the mechanism of progenitor cell mobilization, Jean-Pierre Lévesque and colleagues have examined the role of the chemokine CXCL12 and its receptor CXCR4, both of which are essential for homing and retention of progenitors in the bone marrow. They found (pages 187–196) that mobilization in mice coincides with lower levels of CXCL12 in the marrow on one hand, and cleavage of CXCR4 on the surface of progenitor cells, which renders them unresponsive to CXCL12, on the other. This suggests that inactivation of the CXCR4/CXCL12 pathway by neutrophil-derived proteases might play a critical role in allowing the egress of progenitor cells into the circulation.



Glycosphingolipids and apoptosis. TNF-α induces apoptosis in many different cell types. In some of them, including liver cells, mitochondria play a crucial role in the apoptotic pathway. Ceramide, synthesized in response to TNF-α by two sphingomyelinases, neutral SMase and acidic SMase (ASMase), is a pro-apoptotic signaling intermediate. Having found that ASMase-deficient mice are protected from TNF-α–mediated hepatocellular apoptosis (pages 197–208), José Fernández-Checa and colleagues went on to demonstrate that in response to TNF-α (and promoted by ASMase), not ceramide, but glycosphingolipids, including GD3, are targeted to the mitochondria. They conclude that mitochondrial targeting of glycosphingolipids is likely to be the key event that sets off the apoptotic cascade.



Epigenetic modulation of IGF2. *IGF2*, which encodes a mitogenic peptide, is overexpressed in a variety of tumors, including hepatocellular carcinoma, and thought to stimulate tumor growth in an autocrine fashion. Having previously shown that inhibition of DNA methylation increases *IGF2* transcription from one of its promoters, Andrew Hoffman and colleagues sought to methylate this specific promoter region in the hope of decreasing IGF2 levels and ultimately inhibiting tumor growth. As they report (pages 265–273), treatment with a methylated oligonucleotide that is complementary to the human *IGF2* P4 promoter induced de novo methylation in the P4 region. Moreover, IV injection of the oligo prolonged survival of mice implanted with human hepatocarcinoma cells. Future experiments will determine whether such oligos can be used more generally to manipulate mammalian gene expression and whether they have therapeutic potential in liver cancer.